Fulvestrant- and Palbociclib-Induced Hepatotoxicity in a Patient with Breast Cancer: A Case Report

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BACKGROUND: Fulvestrant and palbociclib are each approved for the treatment of hormone receptor–positive metastatic breast cancer, and these agents can also be used in combination. Cases of hepatotoxicity and elevated liver enzymes have been documented with fulvestrant and with palbociclib when used as single agents.

OBJECTIVE: To describe a real-world patient case with drug-induced hepatotoxicity while using the combination of fulvestrant and palbociclib and consider if the causative agent can be determined.

DISCUSSION: Our patient presented with metastatic breast cancer and no abnormal laboratory results or metastasis to the liver. After 3 months of palbociclib and fulvestrant combination therapy, the patient had elevated transaminases and treatment with this combination was stopped. Retrial of single-agent fulvestrant was re-introduced and shortly after that palbociclib was added back, at a reduced dose of 100 mg. Within 1 week of restarting palbociclib therapy, she had elevation in her liver function again. Fulvestrant and palbociclib are each extensively metabolized by the liver, which may lead to additive toxicity. Over time, this can cause increased burden on the liver and result in hepatotoxicity.

CONCLUSION: Based on the timing of the patient's liver enzyme elevation and recovery, it is possible that palbociclib was the main cause of hepatotoxicity, but toxicity from the dual-agent combination cannot be ruled out. The combination of fulvestrant and palbociclib may have an additive risk for hepatotoxicity; attempts to reduce the dose proved ineffective in this case. In general, these agents are well tolerated with appropriate monitoring and dosing.

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Disclosures at end of text

Fulvestrant is an estrogen receptor (ER) antagonist that works by competitively binding and downregulating ERs on tumor cells and inhibiting tumor growth.[1] This drug is usually used for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer, alone or in combination with palbociclib, in women with breast cancer that has progressed after endocrine therapy.[1]

Palbociclib is a reversible small-molecule cyclin-dependent kinase (CDK) inhibitor that is selective for CDK4 and CDK6.[2] CDKs regulate cell-cycle progression at the G1/S phase by blocking retinoblastoma hyperphosphorylation.[2] Combining palbociclib with an anti-estrogen, such as fulvestrant, allows for greater inhibition of retinoblastoma phosphorylation, downstream signaling, and tumor growth compared with either drug alone.[2,3]

A standard dosing regimen of fulvestrant consists of an initial dose of 500 mg on days 1, 15, and 29, followed by a maintenance dose of 500 mg once monthly.[1] Patients with moderate hepatic impairment (Child-Pugh class B) require a dose reduction, and the initial and maintenance dose should be reduced to 250 mg.[1] The use of fulvestrant has not been assessed in patients with severe hepatic impairment (Child-Pugh class C).[1] Some of the side effects of fulvestrant include fatigue, headache, hot flashes, stomatitis, anemia, and hepatotoxicity. Increased liver enzymes occur in >15% of patients taking this agent.[1]

Periodic liver function tests are recommended in patients taking fulvestrant, because of the high rate of hepatotoxicity.[4] Fulvestrant 250-mg dose has a half-life of 40 days in adults and is extensively metabolized in the liver through multiple biotransformation pathways, including cytochrome (CY)P3A4, which is involved in the oxidation pathway. Hepatitis and liver failure have been reported in postmarketing experience, occurring in <1% of the patients who have taken this drug.[1,4]

Clinical trials leading to the approval of fulvestrant

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Table 1 Patient's Home Medication List

Drug	Dose
Omeprazole	20 mg, oral, once daily
Levothyroxine	175 mcg, oral, once daily, with breakfast
Denosumab	120 mg, subcutaneous injection, once monthly
Amlodipine	5 mg, oral, once daily
Ondansetron	Orally disintegrating tablets, 8 mg, every 8 hrs, as needed for nausea or vomiting
Ibuprofen	200 mg, oral, as needed for pain

did not report hepatotoxicity, including the postmarketing CONFIRM phase 3 trial.[1,5] However, a case report by Dziamski and colleagues describes a patient with metastatic breast cancer who had normal liver function test results at baseline and slight elevation in alkaline phosphatase of 170 U/L.[6] After initiation of fulvestrant, this patient had extremely high levels of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio of 734/950, total bilirubin of 6.3 mg/dL, and an alkaline phosphatase of 1093 U/L. Previous liver disease, alcohol use, and other hepatotoxic medications were all ruled out.[6] Although the incidence of liver injury and hepatotoxicity with the use of fulvestrant may be rare, this case report suggests that fulvestrant may induce these adverse events.

A standard dose of palbociclib consists of 125 mg orally daily for 21 days and then 7 days off (repeated once every 28 days).[2] If a patient has adverse events while taking palbociclib, a dose reduction to 100 mg daily is appropriate, and further reduction may be considered, depending on the patient. Mild-to-moderate hepatic impairment (Child-Pugh A and B) does not require a dosage adjustment, whereas severe hepatic impairment (Child-Pugh C) recommends a dosage reduction to 75 mg once daily for 21 days, followed by 7 days off the drug.[2]

Some side effects seen with palbociclib include neutropenia, thrombocytopenia, and increased liver enzymes.[2] Serum AST and ALT elevations are seen in many patients. Similar to fulvestrant, palbociclib, with a half-life of 29 hours, is mainly metabolized in the liver, primarily through CYP3A and sulfotransferase (SULT) enzyme SULT2A1.[2] Clinical trials leading to the approval of palbociclib showed abnormalities in liver function tests but did not report events of hepatotoxicity or liver injury.[2]

Vuppalanchi and colleagues reported on 2 patients who had liver failure after treatment with palbociclib plus letrozole.[7] Imaging studies revealed pseudocirrhosis in both patients, and other causes were ruled out.[7] Although the literature is scarce, based on the available case reports and liver function abnormality data reported in clinical trials, it is apparent that fulvestrant and palbociclib each carries risks for liver injury.[1,2,6-8] Therefore, the use of these agents together for breast cancer poses an additive risk for hepatotoxicity.

Our case report involves a patient who had hepatotoxicity and elevations in liver function tests after concurrent treatment with fulvestrant and palbociclib.

Case Report

A 58-year-old postmenopausal woman of Cuban descent noticed a lump in the inner lower quadrant of her right breast in 2014 but did not present for evaluation until April 2016. The patient's medical history included hypothyroidism, hypertension, and hypoglycemia. Her surgical history included left breast excisional biopsy in 1980, appendectomy at approximately age 12 years, and bilateral tubal ligation. Her family history included thyroid cancer (ie, her maternal aunt, in her 50s) and 1 maternal first cousin with cervical cancer at age 32 years.

The patient is an ex-smoker, with an 8 pack-year history (she quit smoking in 1994). Her home medications include ondansetron tablets, 8 mg orally every 8 hours, as needed for nausea or vomiting; omeprazole 20 mg, orally, once daily; oral ibuprofen 200 mg, as needed; oral levothyroxine 175 mcg once daily, with breakfast; subcutaneous denosumab 120 mg once monthly; and amlodipine 5 mg, orally, once daily (**Table 1**).

She had not been using any complementary or alternative medications, including herbal supplements, that could have affected the metabolism of these agents. Our review revealed no drug interactions between the patient's prescriptions and fulvestrant or palbociclib, except for a possible interaction with palbociclib and amlodipine. Although palbociclib may increase the serum concentration of CYP3A4 substrates, this agent is a weak, time-dependent inhibitor of CYP3A4, which likely makes this drug interaction clinically insignificant.[2] Monitoring of the patient showed no apparent issues related to increased amlodipine concentrations.

A mammogram that was ordered at the time of the patient's presentation and was performed in April 2016 revealed a lobular, noncalcified 3.7-cm mass adjacent to the nipple, along with a small amount of dimpling in the skin. An ultrasound-guided core needle biopsy performed in May 2016 revealed a grade 2 invasive ductal carcinoma with moderate differentiation. The invasive carcinoma was 14 mm, and molecular and hormonal testing revealed it was 100% ER-positive, 95% progesterone receptor–positive, and HER2-negative at 1+ via immunohistochemistry. A biopsy of the right axillary lymph node revealed fibroadipose tissue with fat necrosis.

At presentation, the patient also complained of back

discomfort and was therefore sent for a staging study with positron-emission tomography (PET) and computed tomography (CT) in May 2016. The PET-CT imaging revealed a 4.2-cm lesion in the low-right neck to the right of midline arising from the thyroid gland, as well as avid bone marrow lesions, suggestive of bone metastasis involving C2, T3, T10. Pathology results from the CT-guided biopsy of T3 were consistent with metastatic adenocarcinoma and necrosis. The tumor cells expressed estrogen at 60% and progesterone at 40%, and were negative for HER2, which was consistent with metastatic breast cancer to the bone. In addition, the CT scan revealed hepatic steatosis but no liver lesions. The patient was diagnosed with T3N1M1 stage IV cancer of the right breast and was initiated treatment with daily letrozole 2.5 mg, orally, on July 6, 2016.

The patient also received radiation therapy to vertebrae C1-C3, T2-T4, and T9-T11, which began in August 2016 and was completed in September 2016. During radiation, letrozole therapy was stopped and was restarted on September 3, 2016. Unrelated to her breast cancer, the patient underwent a partial thyroidectomy for what was believed to be a large goiter. Pathology analysis revealed papillary thyroid cancer, and the patient had a complete thyroidectomy in December 2016. In early March 2017, a restaging PET scan revealed disease progression in the right breast and a possible new rib lesion.

The PET scan revealed no liver lesions. At this time, letrozole therapy was discontinued and the oncology team decided to begin combination therapy with fulvestrant and palbociclib. The patient's baseline laboratory test results from February 13, 2017, were within normal limits (**Table 2**). The patient began to receive fulvestrant on March 8, 2017; 1 month later, palbociclib therapy was initiated. Fulvestrant was dosed at 500 mg intramuscularly on days 1, 15, and 29, followed by maintenance therapy of 500 mg intramuscularly, repeated once monthly. The first dose of palbociclib was administered on April 5, 2017, at 125 mg, orally, once daily for 21 days, which was repeated every 28 days.

The patient had no history of elevated liver enzymes or jaundice at baseline. She completed the first 3 months of combination therapy with palbociclib and fulvestrant (**Table 3** and **Figure**) without incident or adverse events; a CT scan showed no liver metastasis on June 21, 2017. The patient received the last dose of fulvestrant on May 31, 2017, and completed her last dose of palbociclib on June 16, 2017. Follow-up laboratory values taken on June 23, 2017, revealed elevation of liver aminotransferases that continued to increase and peaked on July 3, 2017, with ALT >700 and AST 421. The patient's total bilirubin remained stable. At this time, it was decided to place palbociclib and fulvestrant treatment on hold (Table 3).

Table 2 Patient's Baseline Laboratory Results

Baseline laboratory tests (normal range)	Test results on 2/13/17
Bilirubin, total (0.0-1.2), mg/dL	0.7
Alkaline phosphatase (39-117), IU/L	86
AST (0-40), IU/L	18
ALT (0-32), IU/L	29
Glucose (65-99), mg/mL	81
BUN (6-24), mg/dL	16
Creatinine (0.57-1.00), mg/dL	0.62
Estimated GFR non–African American (>59), mL/min/1.73	101
BUN/creatinine ratio (9-23), mg/dL	26 (H)
Sodium (134-144), mmol/L	139
Potassium (3.5-5.2), mmol/L	4.3
Chloride (96-106 L), mmol/L	103
CO_2 (18-29), mmol/L	20
Calcium (8.7-10.2), mg/dL	9.8
Protein, total (6.0-8.5), g/dL	7.5
Albumin (3.5-5.5), g/dL	4.1
WBCs (3.4-10.8), × 10^3/µL	9.8
RBCs (3.77-5.28), × 10^6/µL	4.85
Hemoglobin (11.1-15.9), g/dL	13.1
Hematocrit (34.0-46.6), %	39.2
Platelets (150-379), × 10^3/µL	197
Neutrophil antibody (1.4-7.0), × 10^3/µL	8.1 (H)

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO_2, carbon dioxide; GFR, glomerular filtration rate; (H), high; RBCs, red blood cells; WBCs, white blood cells.

She had hepatologic evaluation and the elevation of liver enzymes was presumed to be drug induced. Tests for markers of acute hepatitis (A, B, and C) all had negative results, as did immunoglobulin (Ig)G and antinuclear antibodies (ANAs) tests, with the smooth muscle only slightly above the upper limits of normal, as indicated by laboratory tests drawn on July 3, 2017 (**Table 4**).

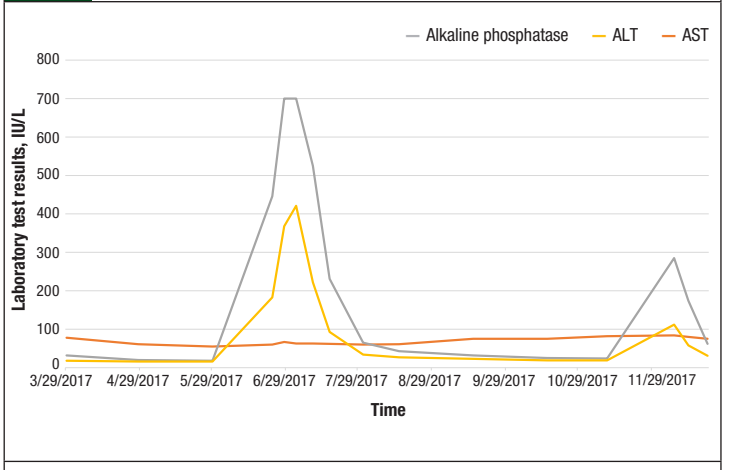
At this time, it was unclear if the hepatotoxicity was a result of the fulvestrant, the palbociclib, or a cumulative toxicity from the 2 drugs. Restaging scans revealed stable disease, and the liver function returned to baseline, as was demonstrated by laboratory test results on August 15, 2017. The patient restarted single-agent therapy with fulvestrant on August 24, 2017, dosed at 500 mg intramuscularly, repeated once every month. Restaging scans in November 2017 revealed borderline

Table 3 Timeline of Laboratory Test Results Related to Drug Initiation and Discontinuation

Laboratory test results (normal range)	3/8/17 fulvestrant initiated; 4/5/17 last dose of palbociclib (F + P)[a] 4/28/17	(F + P)[a] 5/26/17	5/31/17 Last dose of fulvestrant; 6/16/17 last dose of palbociclib (F + P)[a] 6/23/17	(Treatment held) 6/28/17	7/3/17	7/10/17	7/17/17	7/31/17	8/15/17	8/24/17 fulvestrant restarted (F) 9/15/17	(F) 10/16/17	(F) 11/10/17	11/30/17 palbociclib restarted at reduced dose of 100 mg (F + P)[a] 12/8/17	12/10/17 fulvestrant and palbociclib permanently discontinued 12/14/17	12/22/17
Bilirubin, total (0.0-1.2), mg/dL	0.4	0.4	0.6	0.7	0.7	0.6	1.0	0.8	0.6	0.5	0.4	0.4	0.6	0.5	0.5
Alkaline phosphatase (39-117), IU/L	61	55	60	67	63	63	62	60	61	75	75	82	84	80	75
ALT (0-32), IU/L	20	18	446 (H)	>700 (H)	>700 (H)	525 (H)	231 (H)	65	43	32	25	24	285 (H)	174 (H)	62 (H)
AST (0-40), IU/L	16	16	183 (H)	368 (H)	421 (H)	222 (H)	93 (H)	34	27	23	19	19	112 (H)	58 (H)	31

[a]F + P indicates combination therapy with fulvestrant and palbociclib, except between 8/24/17 and 11/30/17, when fulvestrant was used as monotherapy, until palbociclib was restarted at a reduced dose on 11/30/17.
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; F, fulvestrant; (H), high; P, palbociclib.

Figure Hepatic Function Timeline



ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

Table 4 Patient's Hepatitis Panel Results

Hepatitis panel components (normal range)	Test results on 7/3/17
Hepatitis A antibody, IgM	Negative[a]
Hepatitis B core antibody, IgM	Negative[a]
Hepatitis C antibody, s/co ratio (0.0-0.9)	<0.1
Hepatitis B surface antigen	Negative[a]
IgG (700-1600), mg/dL	1368
Smooth muscle, units (0-19)	29 (H)
Antinuclear antibody	Negative[a]

[a]Negative indicates the results were normal.
(H) indicates high; IgG, immunoglobulin G; IgM, immunoglobulin M; s/co, signal-to-cutoff.

disease progression, with a 1.6-cm lesion in the left lobe of the liver, as well as new right axillary adenopathy suspicious of malignancy. On November 30, 2017, the patient restarted treatment with palbociclib in combination with fulvestrant at the reduced daily dose of 100 mg, for 21 days, and repeated every 28 days.

One week later, the patient presented with elevated liver enzymes and the combination treatment with palbociclib plus fulvestrant was stopped; the last dose of fulvestrant was on November 16, 2017, but palbociclib therapy was continued until December 10, 2017, when it was also permanently discontinued. Once her liver function began to trend toward normal after 4 weeks, as seen on the laboratory results from December 22, 2017 (Table 3), the patient was evaluated for participation in a clinical trial, but was found to be ineligible because of her thyroid cancer history.

On December 26, 2017, the patient was started

Table 5 Patient's Liver Function While Receiving Subsequent Agents: Tamoxifen Followed by Albumin-Bound Paclitaxel

	Date of test results							
Laboratory results (normal range)	12/26/17 tamoxifen started ↓ 1/9/18	1/26/18	2/8/18	2/18/18 tamoxifen discontinued; 2/19/18 albumin-bound paclitaxel started ↓ 2/19/18	3/6/18	3/20/18	4/4/18	4/17/18
Bilirubin, total (0.0-1.2), mg/dL	0.6	0.5	0.4	0.4	0.5	0.6	0.6	0.6
Alkaline phosphatase (39-117), IU/L	62	65	63	75	73	106	99	94
ALT (0-32), IU/L	30	28	26	24	25	23	29	29
AST (0-40), IU/L	26	27	25	26	30	38	31	32

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

treatment with tamoxifen 20 mg, taken orally once daily (**Table 5**). Follow-up scans on February 18, 2018, showed rapid disease progression, with new liver lesions. Tamoxifen treatment was therefore discontinued, and the patient began treatment with single-agent albumin-bound paclitaxel at the end of February 2018 (Table 5).

The patient received 8 cycles of albumin-bound paclitaxel until August 10, 2018, when hepatomegaly was diagnosed. New scans revealed disease progression, with new liver metastasis. Albumin-bound paclitaxel was discontinued, and on August 24, 2018, the patient began treatment with oral capecitabine 2000 mg/m^2 daily, divided into 2 doses. Her liver function test results had been slightly elevated (ie, ALT 39 IU/L, AST 36 IU/L) because of the new-onset liver metastasis, but her total bilirubin was within normal limits.

Discussion

The combination of fulvestrant plus palbociclib is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in women whose disease progressed after endocrine therapy.[1,2] The dosing of each of these agents is the same when used in combination and as monotherapy (ie, fulvestrant 500 mg on days 1, 15, and 29, followed by 500 mg once monthly; palbociclib 125 mg once daily on days 1-21, repeated every 28 days).[1,2]

These 2 agents are generally considered to be well tolerated. The most common adverse event associated with palbociclib therapy is hematologic, namely, a decrease in white blood counts (the rate of grade 3 neutropenia is approximately 66%).[2] Other adverse events with palbociclib include fatigue, nausea, diarrhea, and alopecia.[2]

The most common adverse events (>10%) associated with fulvestrant are fatigue, arthralgia, nausea, hot flashes, and injection-site pain.[1] Of note, fulvestrant and palbociclib are associated with large ranges of hepatic adverse reactions. Fulvestrant can lead to increased AST in 5% to 48% of patients, whereas palbociclib can result in increased AST in 8% to 52% of patients.[4,9]

Fulvestrant and palbociclib are extensively metabolized by the liver, and in patients with moderate hepatic impairment (ie, Child-Pugh class B), the average area under the curve of fulvestrant increased by 70% compared with patients with normal hepatic function.[1] This is a possible reason for the additive toxicity seen with the combination of fulvestrant and palbociclib, because these drugs are in competition with each other for metabolism through the liver, which can cause increased burden on the liver and result in hepatotoxicity over time.

Palbociclib was initially approved for first-line treatment, in combination with letrozole, of postmenopausal women with ER-positive, HER2-negative advanced breast cancer based on the results of the PALOMA-1/TRIO-18 randomized phase 2 clinical trial.[9,10] Finn and colleagues reported improved survival outcomes in this study, with a 10-month increase in progression-free survival with palbociclib plus letrozole versus letrozole alone (20.2 months vs 10.2 months, respectively). No cases of liver toxicity were reported in this study.[9]

In the PALOMA-3 clinical trial, Loibl and colleagues evaluated the safety and efficacy of the combination of fulvestrant and palbociclib in patients with HR-positive, HER2-negative advanced or metastatic breast cancer who had previously received endocrine therapy, which also showed positive results.[11] An increase of nearly 4 months was seen for the primary end point of progression-free survival with palbociclib plus fulvestrant versus fulvestrant alone (9.5 months vs 5.6 months, respectively).

No direct hepatic adverse events were reported in this study, but 1 patient who had disease progression also had liver failure.[11] It is unclear if this liver failure was drug-related or disease-related. This is another confounding factor when evaluating the literature for these

2 agents. In addition, 37% of patients receiving fulvestrant plus palbociclib in the PALOMA-3 study had liver metastasis before receiving fulvestrant and palbociclib, which can show decreased liver function or abnormalities on laboratory test results.[11]

The presentation and clinical course of our patient leads to the conclusion that her hepatotoxicity was, in fact, medication-related, most likely caused by the combination of palbociclib and fulvestrant. Based on the final Naranjo score for estimating the probability of an adverse drug reaction, our patient scored a 7, showing that it is probable that this adverse reaction was related to the palbociclib and/or fulvestrant treatment, but it also takes into consideration that other causes may be present.[12]

The patient did not present with abnormal laboratory results or metastasis to the liver at time of diagnosis. She had normal liver function tests at baseline, and only had bone metastasis at the time treatment was initiated with palbociclib and fulvestrant. She completed 3 months of combination therapy before having elevated transaminases, at which point fulvestrant and palbociclib therapy was stopped; the patient had negative markers for hepatitis A, B, and C, along with being IgG-negative.

The patient's ANA test was negative, and the smooth muscle was only slightly above the limit of normal, as was documented by laboratory tests. Retrial of fulvestrant monotherapy was initiated once the liver function test results returned to normal. The patient did not have repeated liver function test elevations until palbociclib was re-introduced 3 months later, at a reduced dose of 100 mg. The elevation in liver function tests occurred within 1 week of initiating palbociclib therapy.

This disease course likely implicates palbociclib as the culprit; however, a combined additive effect of fulvestrant and palbociclib for inducing liver toxicity cannot be ruled out. The dose reduction of palbociclib was not effective at preventing the repetition of the adverse event, and the use of fulvestrant plus palbociclib combination was permanently discontinued.

Conclusion

We are unable to determine whether fulvestrant or palbociclib was the more likely culprit. However, based on the timing of liver enzyme elevation and recovery, it is likely that palbociclib is the main cause of our patient's hepatotoxicity, but dual-agent toxicity from the 2 agents cannot be ruled out. The combination of fulvestrant and palbociclib potentially has an additive risk for hepatotoxicity and attempts to reduce the dose proved ineffective. In general, fulvestrant and palbociclib are well tolerated with appropriate monitoring and dosing. Although the incidence of hepatotoxicity is rare, it is important to assess for baseline risk factors (ie, history of liver disease, alcohol use, and other hepatotoxic medications, including complementary and alternative medications on the patient's profile) in patients who are prescribed combination therapy with fulvestrant and palbociclib. More data are needed to determine the proper action for treatment adjustments, dose reductions, or the potential elimination of one or both agents.

Author Disclosure Statement

Dr Elder, Dr Ohana, and Dr Younas have no conflicts of interest to report.

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